Symptomatic Profile of Cariprazine in the Context of ICD-11 Domains for Schizophrenia: Review of Clinically Oriented Studies

Симптоматический профиль карипразина в контексте доменов шизофрении в МКБ-11: обзор клинически ориентированных исследований

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Review

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ABSTRACT

INTRODUCTION: One of the innovations in the ICD-11grouping "Schizophrenia and Other Primary Psychotic Disorders" is the implementation of six symptom domains intended to improve diagnostics and treatment of these mental conditions in clinical practice. In this respect, evaluation of the effects of various psychotropic drugs, primarily antipsychotic agents, on the specified psychotic symptom domains is a critical task. The antipsychotic agent cariprazine, registered in many countries worldwide (including Russia) for schizophrenia treatment, was selected as the psychotropic drug model for the purposes of the present review.

METHODS: For the purposes of this review the MEDLINE, Cochrane Central Register of Controlled Trials, and PubMed databases were searched for randomized controlled trials comparing cariprazine with a placebo, or a placebo and one or several antipsychotic agents, and that was performed within the period from January 2014 to March 2021.

RESULTS: Cariprazine has proved its efficiency in relation to all symptom groups of the ICD-11 domain "Positive Symptoms", and may be considered a front-line therapy for treatment of the first and multiple episodes of schizophrenia, disorganized thinking, and behavioral disorders in the form of aggressiveness and hostility. Cariprazine has the best evidential base for treatment of various symptoms within the ICD-11 domain "Negative Symptoms" among all antipsychotic agents. The data with regard to the effects of cariprazine on the domain "Depressive Mood Symptoms" are controversial. No data concerning the effects of cariprazine on the domain "Manic Mood Symptoms" are available, but the effectiveness of cariprazine monotherapy for manic episodes without any psychomotor agitation signs in the instance of bipolar disorder has been demonstrated. The effectiveness of cariprazine therapy for the ICD-11 domain "Psychomotor Symptoms" has not been investigated, either within the framework of monotherapy or in the course of adjuvant therapy. The effectiveness of cariprazine has been demonstrated in treatment of the domain "Cognitive Symptoms", and the pro-cognitive effect of the drug has developed regardless of its impact on any other schizophrenia symptoms. The drug's capability to improve the functioning of patients with schizophrenia was demonstrated regardless of the impact on psychotic symptoms.

CONCLUSION: Cariprazine is the first-line drug for treatment of the domain "Negative Symptoms" as well as representing front-line therapy for the treatment of ICD-11 domains "Positive Symptoms" and "Cognitive Symptoms". Additional studies will be required in order to evaluate the effects of cariprazine on the ICD-11 domains "Manic Mood Symptoms" and "Depressive Mood Symptoms".

АННОТАЦИЯ

ВВЕДЕНИЕ: Одним из нововведений раздела МКБ-11 «шизофрения и другие первичные психотические расстройства» является имплементация 6 дополнительных доменов, которые должны улучшить диагностику и лечение данных состояний в клинической практике. В связи с этим, актуальной задачей является оценка влияния различных психотропных средств, в первую очередь, антипсихотиков, на выделенные домены психотических расстройств. В данном обзоре в качестве психотропного средства был выбран антипсихотик карипразин, который зарегистрирован во многих странах мира, включая Россию, для лечения шизофрении.

МЕТОДЫ: Для данного обзора был осуществлен поиск рандомизированные контролируемых исследований, сравнивающих карипразин или с плацебо, или с плацебо и одним или несколькими антипсихотиками по базам MEDLINE, Cochrane Central Register of Controlled Trials и PubMed, выполненных с января 2014 по март 2021 года.

РЕЗУЛЬТАТЫ: Карипразин доказал свою эффективность в отношении всех групп симптомов домена МКБ-11 «позитивные симптомы» и может рассматриваться как препарат выбора при лечении первых и множественных эпизодов болезни, дезорганизации мышления и нарушенного поведения в виде агрессии и враждебности. Карипразин имеет наилучшую среди всех антипсихотиков доказательную базу для лечения разных симптомов домена МКБ-11 «негативные симптомы». Данные о влиянии карипразина на домен «депрессивные симптомы являются противоречивыми. Отсутствуют данные о влиянии карипразина на домен «маниакальные симптомы», но доказана эффективность монотерапии карипразином маниакальных эпизодов без признаков психомоторного возбуждения при биполярном расстройстве. Исследования эффективности терапии карипразином домена МКБ-11 «психомоторные симптомы» не проводилось ни в рамках монотерапии, ни в рамках адьювантной терапии. Карипразин доказал эффективность в лечении домена «когнитивные симптомы» и прокогнитивный эффект препарата развивался независимо от его влияния на другие симптомы шизофрении. Была показана возможность препарата улучшать функционирования больных шизофренией, независимо от влияния на симптомы заболевания.

ВЫВОДЫ: Карипразин является препаратом первого выбора при лечении домена «негативные симптомы», а также препаратом выбора при лечении доменов МКБ-11 «позитивные симптомы» и «когнитивные симптомы». Необходимы дополнительные исследования для оценки влияния карипразина на домены МКБ-11 «маниакальные симптомы» и «депрессивные симптомы».

Keywords: *cariprazine; schizophrenia; ICD-11; symptom domains; PANSS*
Ключевые слова: *карипразин; шизофрения; МКБ-11; домены первичных психотических расстройств; PANSS*

INTRODUCTION

The main reason for the introduction of statistically identifiable psychopathological symptom groups or domains into clinical practice was the desire to reduce the clinical heterogeneity of schizophrenia, to describe the clinical pattern of the disease more comprehensively, and to identify homogeneous groups of patients for neurobiological research.[1] The following five dimensions are usually specified in studies of the dimensional structure of mental diseases: “positive symptoms”, “negative symptoms”, “cognition”, “disorganization”, and “affective symptoms”.[2] Drug abuse, early manifestation of the disease, absence of insight, cognitive functioning, hostility, behavioral disorders,

and "motor symptoms" are considered to represent additional domain.[2]

Dimensional models based on the PANSS scale (Positive and Negative Symptom Scale) have become widespread in psychiatry.[3] Although only three PANSS domains were initially identified by the authors (the sub-scales of positive and negative syndromes and general psychopathology),[3] other PANSS models were proposed in subsequent studies. In particular, these are the pyramidal model with the specification of negative, positive, and depressive symptoms,[4] the five-factor Marder model (positive symptoms, negative symptoms, disorganization of thinking, hostility/agitation, and anxiety/depression)[5] and others, yet none of these are fully satisfactory.[6] This is apparently related to the fact that many variables (age, duration and phase of the disease, drug administration, etc.) can affect the symptoms of schizophrenia, and the same patients may fall into different groups in different models.

In ICD-11, dimensional evaluation is possible for disorders within the grouping "Schizophrenia and Other Primary Psychotic Disorders" (schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, any other primary psychotic disorders) as supplementary or additional according to the classification "for a better understanding of the condition and treatment selection".[7] It is important to note that although the term "dimensional evaluation" is present in ICD-11, the term "dimension" itself is not used therein, and the terms "domain", "symptomatic manifestations", and "symptom qualifiers" can be found in a similar context. Six groups of symptomatic manifestations (domains) are proposed in ICD-11 for primary psychotic disorders: psychotic, negative, depressive mood, manic mood, psychomotor, and cognitive symptoms.[7] Only negative, depressive mood, manic mood, and psychomotor symptoms fully coincide in ICD-11 and DSM-5.[8,9] Two dimensions correspond to the ICD-11 domain "Psychotic Symptoms" in DSM-5: "hallucinations" and "delusional ideas", and the dimension "cognition reduction" corresponds to the domain "Cognitive Symptoms". The dimension "speech disorganization" is also absent in ICD-11. Each ICD-11 domain may be evaluated according to the following scale: 0 — no symptoms; 1 — symptoms are present, but only in mild form; 2 — symptoms are present in moderate form; 3 — symptoms are present in severe form; 9 — evaluation is impossible on the basis of the available data.[7] As in DSM-5, examples of the evaluation of the severity of the symptoms are given in ICD-11: for example, a severe degree of psychotic symptom manifestation assumes that delusional ideas determine the patient's behavior and disturb his/her functioning considerably. The dimensional approach implemented in the revisions of the two main international classifications in many ways represent the scientific paradigm shift with regard to conceptualization of psychotic disorders. This transition should be gradual, and requires a clear understanding of its basic principles by specialists.[9] The online survey of the Russian psychiatrists' attitudes in relation to ICD-11 showed their interest in ICD-11, especially among young colleagues.[10]

Cariprazine is a partial D2/D3 receptor agonist with primary affinity to the D3 receptor, and produces a multi-functional effect on various types of 5-HT receptor.[11] Partial agonism in relation to D2 receptors is associated with treatment of positive and maniacal symptoms and a low frequency of "dopamine" side effects, such as extrapyramidal syndrome and hyperprolactinemia.[11–13] Blockade of D3 receptors is associated with the pro-cognitive, anti negative and antidepressive properties of the drug.[14] Further, a hypothesis was suggested that a high affinity of the drug to D2 and D3 receptors might enhance its antipsychotic activity and improve the treatment of negative and cognitive symptoms.[15] It was demonstrated with the use of animal models that partial agonism in relation to D3 receptors had a positive effect on cognitive deficiency and anhedonia.[16] Cariprazine also acts as a partial 5-HT1A receptor agonist and as a 5-HT2B, 5-HT2C, and 5-HT7 receptor antagonist.[12] Partial agonism in relation to 5HT1A can have a positive effect on negative and affective symptoms. Antagonism in relation to 5-HT2C and 5-HT7 may be associated with pro-cognitive and antidepressive properties of cariprazine.[17,18] The elimination half-life of cariprazine is approximately 2–4 days, and for its active metabolite (didesmethylcariprazine), this period amounts to 1–3 weeks; therefore, the drug's concentration in the plasma continues to increase for about a week despite the drug being administered in the same dose, and complete elimination of the drug from the blood after ending its administration can take up to several weeks.[12]

Inclusion of the dimensional evaluation of the primary psychotic disorders within ICD-11 will result in the need to assess the effects of various psychotropic drugs,

primarily antipsychotic agents, on the specified psychotic disorder domains. The antipsychotic agent cariprazine, registered in many countries worldwide (including Russia) for schizophrenia treatment, was selected as the psychotropic drug model for the purposes of the present review. In spite of the fact that the pharmacological profile of cariprazine is associated with effects on the positive, manic, negative, cognitive, and depressive symptoms, and its influence on various schizophrenia symptoms has been demonstrated by randomized clinical trials, the drug's efficiency with regard to the identified ICD-11 domains has never previously been evaluated.

The purpose of this article is to assess the efficiency of the effects of cariprazine on the ICD-11 domains identified for schizophrenia on the basis of clinically oriented studies, primarily randomized clinical trials.

METHODS

A search of English language publications for the current review was carried out with the use of the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed databases. The search was performed according to the following keywords: "Schizophrenia" or "Psychosis" and "Cariprazine". The following inclusion criteria were adopted: trials based on the referred sample of adults; reliable diagnostics of schizophrenia; and structured interviews and standardized criteria based on reliable assessments of the results. Firstly, the final analysis included published randomized controlled trials that compared the effects of cariprazine with a placebo, or with a placebo and other antipsychotic agents, in the course of short-term and long-term therapy of various schizophrenia symptoms performed within the period from 2014 (when the first randomized controlled trials evaluating cariprazine efficiency in schizophrenia treatment were published) to June 2021. Secondly, the data from randomized controlled trials were used for analysis by means of post-hoc evaluation; the results of meta-analyses assessing the efficiency and safety of different antipsychotic agents, particularly cariprazine, in the treatment of various schizophrenic symptoms. Thirdly, randomized controlled trials of cariprazine's efficiency in the acute treatment of mania and depression in the frame of bipolar disorder were used in the review in order to assess the drug's effects on the ICD-11 domains "Depressive Mood Symptoms" and "Manic Mood Symptoms". Descriptions of the symptom domains were taken from the English language version of Chapter 6 of the International Classification of Diseases, Rev. 11 (ICD-11).

CARIPRAZINE'S EFFECTS ON THE DOMAIN "POSITIVE SYMPTOMS"

The ICD-11 domain "Positive Symptoms of Primary Psychotic Disorders" includes not only persistent delusional ideas, hallucinations, and severe behavioral disorders, but also disorganized thinking, which is considered an individual dimension of primary psychotic disorders in DSM-5.[8]

The efficiency of cariprazine within the framework of remitative therapy for schizophrenia was demonstrated by three double-blind placebo-controlled six-week multi-center trials (Table 1).

Table 1. Short-term studies of cariprazine efficiency for remitative therapy of schizophrenia

Trial 1 (Durgam et al., 2014)		**Trial 2 (Durgam et al., 2015)**		**Trial 3 (Kane et al., 2015)**	
Multi-center randomized double blind placebo-controlled					
Duration: total 9 weeks (wash-out period — 4–7 days; therapy period — 6 weeks; observation period — 2 weeks)					
5 groups		4 groups		3 groups	
N=732	PANSS score reduction	N=617	PANSS score reduction	N=440	PANSS score reduction
Fixed:		**Fixed:**		**Fixed/ variable:**	
Placebo	11.8	Placebo	14.3	Placebo	16.0
Cariprazine 1.5 mg	19.4	Cariprazine, 3 mg	20.2	Cariprazine, 3–6 mg	22.8
Cariprazine 3.0 mg	20.7	Cariprazine, 6 mg	23.0	Cariprazine, 6–9 mg	25.9
Cariprazine 4.5 mg	22.3	Aripiprazole, 10 mg	21.2		
Risperidone 4 mg	26.9				

Primary end point: total score as per the PANSS scale in 6 weeks

Additional end points: scores as per NSA-16, CGI-I, PANSS (positive/negative symptoms), SQLS-R4, CDR/CTT scales

In the first trial (Durgam et al., 2014), to assess cariprazine's safety and efficiency, 732 patients were randomized into placebo, cariprazine (fixed doses of 1.5, 3.0, and 4.5 mg) or risperidone (4 mg) groups.[19] By the end of the trial, all the cariprazine and risperidone doses were found to have caused statistically significant (as compared with the placebo) reductions of the total score (-19.4, 20.7, 22.3, and 26.9, respectively) and considerable improvement according to the Clinical Global Impression Scale (p<0.05).[19]

During the second trial (Durgam et al., 2015), the patients took either a placebo (n=153), or fixed doses of cariprazine (3 mg/d and 6 mg/d), or an active comparator, aripiprazole (10 mg/d).[20] As in the previously mentioned trial,[19] a larger dose of cariprazine can be associated with a greater reduction in the total score, as per the PANSS scale (20.2 and 23.0, respectively) as well as the scale of positive symptoms (6.8 and 7.5 points, respectively) and the PANSS scale of general psychopathology (9.6 and 11.3 points, respectively). Further, the patients taking the active substance demonstrated significant improvement with regard to reduction of negative symptoms and depressive mood in comparison with the placebo, as measured via the use of the PANSS scale of negative symptoms and the NSA-16 scale for evaluation of negative symptoms. Improvements according to the CGI-S Scale were also considerably greater for both doses of cariprazine beginning from the second week of therapy.[20]

Efficiency, safety, and tolerability of two cariprazine administration regimes (3–6 mg and 6–9 mg respectively) for patients showing the manifestation of schizophrenia were assessed during the third nine-week trial (Kane et al., 2015) performed within the framework of the third drug registration stage.[21] Statistically significant differences in favor of the active substance were observed by the sixth week of therapy for the PANSS scales of positive and negative symptoms (3–6 mg/d, p<0.05; 6–9 mg/d, p<0.001) and the Clinical Global Impression Scale CGI-S (3–6 mg/d, p<0.05; 6–9 mg/d, p<0.001). The statistical difference compared to the placebo according to PANSS began to be observed from the first week of therapy onward for the group taking 6–9 mg of cariprazine, and from the second week of drug administration for the group taking 3–6 mg. In accordance with the CGI-S Scale differences, as compared with the placebo, began to be observed from the first week of therapy for the patients taking 6–9 mg of cariprazine, and from the third week for 3–6 mg.[21]

Post-hoc analysis of cariprazine's effects (the doses of 1.5–9 mg) on the five PANSS domains identified[5] and individual points of this scale[22] (see Table 2) were performed on the basis of these three trials including 1466 patients with schizophrenia.

By the end of the sixth week of therapy, cariprazine was clearly superior to the placebo for all five PANSS domains identified in a statistically reliable manner. Statistically significant differences between cariprazine and the placebo with regard to reduction of individual symptoms as per the PANSS scale were determined for 26 out of 30 points of this scale (that is, with the exceptions of G1, G3, G7, P5). The average effect size for treatment of positive symptoms was 0.38: it was the most prominent for the dose of 4.5 mg (effect size of 0.52) and the least prominent for 1.5 mg (effect size of 0.25). Cariprazine was superior to the placebo in the treatment of the symptoms within the domain "Disorganization of Thinking''[5] by 46.7% on average; in this instance, the effect size was the most prominent for the dose of 4.5 mg (0.6) and the least prominent for 3 mg (0.38).[22] Taking into account the description of the domain "Positive Symptoms" in ICD-11, only points P2 (conceptual disorganization) and N5 (abstract thinking difficulties) from among the points of this domain may be classified as positive symptoms. Cariprazine was superior to the placebo in the treatment of the domain "Hostility/ Agitation''[5] by 34.8% on average, though to a greater degree for the dose of 1.5 mg and a lesser degree for the dose of 4.5 mg. P4 (agitation) and P7 from this domain may be classified as positive symptoms according to the ICD-11 definitions. The effects of cariprazine on manifestations of aggressiveness and hostility in the instance of schizophrenia through changes in "Hostility" (Point P7) with regard to PANSS by the end of the sixth week of therapy was investigated in a separate study.[23] Statistically significant differences in comparison with the placebo were observed for the patients taking cariprazine, with an initial score of 2 or 3 for Point P7 as early as the first week and up to the end of the trial, while in case of the initial score of 4 and higher statistically significant improvement in favor of cariprazine was observed from only the third week of therapy. By the end of the sixth week of therapy, a higher initial score for Point P7 was associated with an increased reduction in hostility.

Table 2. Changes in the effect size for individual points of the PANSS scale by the end of the sixth week of therapy with different cariprazine doses

	Cariprazine dose				
Identified domains and PANSS points	**1.5 mg**	**3.0 mg**	**4.5 mg**	**6.0 mg**	**1.5–9.0 mg**
Positive symptoms P1 P3 P5 P6 N7 G9 G12	0.25	0.32	0.52	0.42	 0.32 0.2 0.07 0.35 0.23 0.32 0.30
Negative symptoms N1 N2 N3 N4 N6 G7 G16	0.44	0.34	0.62	0.51	 0.25 0.36 0.31 0.37 0.28 0.08 0.38
Disorganization of thinking N5 G5 G10 G11 G13 G15 P2	0.4	0.38	0.6	0.49	 0.26 0.15 0.27 0.36 0.25 0.3 0.44
Hostility/ agitation G14 P4 P7 G8	0.39	0.33	0.31	0.36	 0.23 0.25 0.28 0.34
Anxiety/ depression G2 G3 G4 G6	0.15	0.1	0.15	0.29	 0.18 0.02 0.26 0.17

The duration of the period up to relapse development (obvious aggravation of symptoms, admission to a mental hospital, aggressive behavior or suicidal risks) was selected as the primary end point for the randomized double blind placebo-controlled trial of the efficiency of different cariprazine doses (3, 6, and 9 mg) for stable patients with schizophrenia which lasted up to 72 weeks, where the total score as per the PANSS scale, whilst other scales was used as additional measures.[24] In the course of the observations, recrudescence occurred twice more rarely in the cariprazine group than in the placebo group (24.8% and 47.5%, respectively, the risk ratio — 0.45). The difference between the groups became significant from the eighth week of therapy. By the end of the observation period, the total score as per PANSS, CGI-S, NSA-16, and PSP scales had deteriorated to a greater extent for the placebo group as compared with the cariprazine group. It is also important to note that within the first four weeks of therapy, relapse occurred in only 3% of the patients in the placebo group, which might imply the residual antirelapsing effect of cariprazine partially associated with its long half-life to elimination from the body; its metabolite (didesmethylcariprazine) took 8.4 days to be eliminated. Further, administration of cariprazine is associated with considerably longer persistent remission and increased probability of persistent remission exceeding six months, as compared with the placebo.[25]

Studies of cariprazine in routine clinical practice within the framework of the non-blind trial for the patients with schizophrenia without any response to previous therapy demonstrated that cariprazine administration was associated with significant positive changes beginning from the second week of therapy, and lasting until the

end of the trial (sixteenth week of treatment).[26] By the end of the trial, considerable improvement was observed in 38% of the patients, minimum improvement in 35% of the patients, and no improvement in 11% of the patients. It was also shown that not only was there a considerable reduction in the negative symptoms, but also a reduction in delusions and hallucinations over the course of the trial, which was evaluated via the use of the special-purpose questionnaire, including also questions about case histories and clinical appraisal. In this case, 70% of doctors participating in the trial were satisfied with cariprazine's efficiency.[26]

Comparison of cariprazine with 31 other antipsychotic agents demonstrated that the drug was superior to placebos in the treatment of positive symptoms (the standardized mean difference (SMD) was equal to 0.3; cariprazine took a medium position with regard to this parameter, having almost half the efficiency of the leading antipsychotic agents (amisulpride, risperidone, clozapine).[27] At the same time, cariprazine is superior to many antipsychotic agents with regard to such significant side effects as weight gain, and increases in prolactin and sedation. The authors of this study believe that in spite of the difference in efficiency between antipsychotic agents with regard to reduction of positive symptoms, the focus in therapy selection should be on investigation of the side effect profile where the differences between the drugs is quite evident. Subsequent to investigation of the entire symptom range, including the doses of antipsychotic agents, transition strategies, therapy duration, the role of concomitant therapy, and tolerability, the consensus amongst experts is to recommend the use of cariprazine as the front-line therapy for the treatment of patients with schizophrenia suffering from acute psychotic states (including the first psychotic episode) with attendant agitation and insomnia (in combination with benzodiazepines), metabolic syndrome, and concurrent drug abuse.[28]

The majority of experts recommend maintaining a dose of 1.5–3 mg/day to treat a first psychotic episode, while rapid increase of the dose to the maximum (6 mg/day) is possible in cases of more severe psychotic symptoms.[28] In the case of resistant schizophrenia or cariprazine monotherapy for schizophrenic patients with attendant agitation, the majority of experts recommend rapidly increasing the dose of cariprazine to 6 mg/day. For patients with concomitant metabolic syndrome, experts often recommend a dose of 3 or 4.5 mg/day.[28]

CARIPRAZINE'S EFFECT ON THE DOMAIN "NEGATIVE SYMPTOMS"

The modern concept of negative disorders includes the identification of five particular symptoms (abulia, anhedonia, lack of social activity, blunted affect, alogia) associated with functional reduction.[29] In ICD-11, the domain "Negative Symptoms of Primary Psychotic Disorders" includes the above-mentioned symptoms, where it is also specified that the symptoms should not be secondary ones in relation to depression, administration of antipsychotic drugs, and positive symptoms.[7] It was demonstrated in the early studies of cariprazine use for schizophrenia treatment[19–21] and subsequent meta-analysis of these studies[30] that reduction of negative symptoms against the background of cariprazine therapy did not depend on the reduction of positive symptoms, as the difference between cariprazine and the placebo remained statistically significant (the dose of 1.5–3 mg/day, p=0.0322, 4.5–6 mg/day, p=0.038), even after adjustment for changes in positive symptoms.

Post-hoc analysis of the studies with regard to cariprazine efficiency in acute therapy of schizophrenia[19–21] showed that cariprazine was superior to the placebo at the end of the sixth week of treatment by 47.8% on average; in this case, the effect was most prominent for a dose of 4.5 mg (the effect size — 0.62) and the least prominent for a dose of 1.5 mg (the effect size — 0.44).[22] The Factor Score for Negative Symptoms (PANSS-FSNS), also known as the Marder factor, has become increasingly used in recent years to evaluate the manifestation of negative symptoms and their changes in the course of therapy instead of the PANSS scale of negative symptoms; it includes Points N1, N2, N3, N4, N6, G7 and G16 of PANSS.[5] Direct analysis of these points during administration of different cariprazine doses (1.5–9 mg) showed the following changes in the effect size (as compared with the placebo): 0.25; 0.36; 0.31; 0.37; 0.28; 0.08; and 0.38, indicating that cariprazine administration in all doses reduced all symptoms of the Marder factor — with the exception of motor retardation — to a statistically significant extent.[22] The above-mentioned meta-analysis showed that cariprazine demonstrated higher efficiency in cases of predominant negative disorders and short case history, although the studies analyzed did not

distinguish between primary and secondary negative symptoms.[30]

Cariprazine (average dose of 4.5 mg) and risperidone (average dose of 4 mg) were compared in a multinational randomized controlled trial of schizophrenic patients with predominant negative symptoms.[31] The difference between groups, as measured via the use of PANSS-FSNS, was in favor of cariprazine by the end of the trial (p=0.0022, the effect size in favor of cariprazine — 0.31). Post-hoc analysis of this trial showed that administration of cariprazine in comparison with risperidone was associated with more significant improvement for such PANSS points as affect flattening (N1), emotional withdrawal (N2), passive-apathetic social withdrawal (N4), and abstract thinking difficulties (N5), but not lack of lack of spontaneity and flow of conversation (N6) or stereotyped thinking (N7). In addition, these changes were not dependent on positive, depressive symptoms or the extrapyramidal syndrome, as their changes over the course of therapy were minimal.[32] Another post-hoc analysis including placebo, cariprazine, risperidone, and aripiprazole showed that in accordance with the Marder factor (PANSS-FSNS), reduction of negative symptoms by the end of the sixth week was only statistically significant only cariprazine and risperidone, but not for aripiprazole. After adjustment for changes in the positive symptoms in order to exclude any secondary negative symptoms, only cariprazine, but not risperidone and aripiprazole, was considerably superior to the placebo.[33] The conclusion drawn on this basis was that cariprazine had a direct, specific and independent effect on negative symptoms while risperidone apparently had a predominant effect on secondary negative symptoms, reducing together with the positive symptoms.[33]

The capability of cariprazine to exert an effect on negative symptoms within the framework of long-term administration of the drug was also demonstrated in two trials. In particular, according to a non-blind 48-week trial, the PANSS-FSNS parameters reduced within the first eight weeks of therapy (the least-squares mean (LSM) was 9.0 in the eighth week), and were maintained for the subsequent 40 weeks (the LSM was 11.1 in the forty-eighth week).[34] These data were close to the results of another trial lasting for 20 weeks when the negative symptoms were reduced primarily within the first 12 weeks of treatment and then changed only slightly thereafter (the change in LSM was 11.5 by the twelfth week and 12.1 by the twentieth week).[35] On the basis of these trials, one might conclude that cariprazine had proved its efficiency with regard to treatment of the entire range of negative symptoms, both within the framework of acute and maintenance therapy of schizophrenia, and thus represents the first-line drug for treatment of schizophrenia with predominant negative symptoms.[36] This judgment was confirmed by meta-analysis of the efficiency of antipsychotic agents for treatment of schizophrenic patients with prevailing negative symptoms; according to this analysis, only amisulpride and cariprazine were superior to the placebo with regard to the treatment of this patient group to a statistically significant extent. However, while amisulpride simultaneously caused parallel reduction of depressive symptoms, the efficiency of cariprazine did not depend on any other symptoms.[37] Cariprazine may be also used as a second antipsychotic agent in cases when monotherapy with any antipsychotic drug is not sufficiently effective to treat negative symptoms.[28]

At present, cariprazine is considered the first-line drug for treatment for negative symptoms in many international schizophrenia therapy algorithms,[28,36] including the clinical recommendations of the Russian Society of Psychiatrists for the treatment of schizophrenia.[38]

The cariprazine dose for treatment of negative symptoms varies within the range of 1.5–6 mg, but it has been demonstrated that higher doses (4.5–6 mg) are associated with higher efficiency.[22] The majority of experts specify 4.5 mg (50%) or 3 mg (30%) as the optimal dose of cariprazine for treatment of negative symptoms.[28]

EFFECT OF CARIPRAZINE ON THE DOMAIN "DEPRESSIVE MOOD SYMPTOMS"

The signs of the ICD-11 domain "Depressive Mood Symptoms of Primary Psychotic Disorders" do not fully correspond to known depressive episode criteria as they focus on the mandatory presence of low mood and suicidal behavior (for moderate and high severity cases) in the clinical pattern, while other important depressive episode criteria are omitted.[7] In all likelihood, this approach was chosen to allow for clearer differentiation between depressive and negative symptoms, as some of them, for example anhedonia, anergia, abulia and blunted affect, overlap.[39]

Investigation of the PANSS scale domain "Anxiety/ Depression"[5] including anxiety (G2), guilt feelings (G3), tension (G4), and depression (G6) in the course of post-hoc analysis showed that the effect size in the cariprazine group was 0.21 by the sixth week of therapy (for a dose of 6 mg it was 0.29, and for a dose of 3 mg it was 0.1) which was a little less than the average score reduction in other domains, but nevertheless still statistically reliable.[22] The maximum score reduction for this domain was observed during cariprazine administration in a dose of 6 mg per day (effect size of 0.29). At the same time, no statistically significant difference between cariprazine and the placebo was observed for the most important PANSS signs with regard to the ICD-11 domain "Depressive Symptoms": the effect sizes for the points "depression" (G6) and "guilt feelings" (G3) were 0.17 and 0.02, respectively.[22] It is supposed that such an insignificant reduction of the average score may be associated with the initial low score for these PANSS points in the analyzed studies.[40] Cariprazine did not show any difference in comparison to risperidone in terms of reduction of depressive symptoms[31] as measured via the Calgary Depression Schizophrenia Scale (CDSS).[41]

Taking into account the risk of affective disorder manifestation within a year after a diagnosis of schizophrenia increases more than six-fold in comparison with patients without this diagnosis,[42] the proven efficiency of the drug in the treatment of affective disorders represents one of its additional advantages. To date, four randomized clinical trials of cariprazine therapy for depression in the frame of types I and II bipolar disorder have been performed. These trials showed that the drug, in a dose of 1.5–3 mg, reduced the manifestation of nine out of ten points (i.e., with the exception of internal stress) as per the Montgomery -Asberg Depression Rating Scale (MADRS)[43–46] in a statistically reliable manner, and was found to be safe and well-tolerated in the above-mentioned doses.[47] The trials were used as the basis for approval of cariprazine as a monotherapy to treat depression in the frame of bipolar disorder in the US[48] and treatment of depressive episodes in cases of type I bipolar disorder amongst adults in Russia, which was reflected in the updated pack insert for the drug.[49]

Analysis of cariprazine administration in cases of bipolar depression showed that low doses were efficient.[50] In accordance with the updated pack insert for the drug in Russia, the initial dose is 1.5 mg and may be increased to 3 mg (the maximum dose for this indication) by the fifteenth day.[49] Further, the preliminary data also give evidence of cariprazine's efficiency as an adjuvant therapy for monopolar depression.[51]

A comparison of cariprazine with other antipsychotic agents in the treatment of schizophrenia with concommitant depressive symptoms demonstrates a sufficiently high effect size for such patients (0.36), whilst cariprazine itself ranks one of the best among the 32 antipsychotic agents investigated.[43] The possibility of prescribing antipsychotic agents with antidepressive effects for correction of depressive symptoms that are not dependent on any other causes is considered in the modern schizophrenia treatment algorithms,[52] and cariprazine may be apparently included with these drugs. Thus, pharmacodynamic and clinical data give evidence of the strong potential for cariprazine use in cases of schizophrenia with a high proportion of depressive symptoms, but additional studies involving the patients with higher initial scores for depressive PANSS points as assessed by the Calgary Depression Schizophrenia Scale are required for this purpose.[41]

Although there are no recommendations on preferred cariprazine doses for the treatment of schizophrenia with a high proportion of depressive symptoms in the literature, it seems that lower doses of the drug (1.5–3 mg/day) can be used based on observations of treatment of bipolar depression[46] with cariprazine and, indeed, according to the pack insert for the drug.[49]

EFFECTS OF CARIPRAZINE ON THE DOMAIN "MANIC MOOD SYMPTOMS"

The domain "Manic Mood Symptoms of Primary Psychotic Disorders" specified in ICD-11 includes the signs described in the maniacal episode criteria such as euphoria, irritancy, excited or expansive mood, increased purposeless activity, and other symptoms.[7] The effect size in relation of the PANSS domain "Hostility/ Agitation",[5] including the points "insufficient impulsivity control" (G14), "agitation" (P4), "hostility" (P7), and "non-cooperativity" (G8) was 0.35 on average, which was indicative of a sufficient antimaniacal effect of cariprazine on patients with schizophrenia.[22] The degree of reduction in the scores for this domain was approximately the same for regardless of cariprazine dose. Three trials demonstrated cariprazine efficiency for the patients with maniacal or mixed episodes in the

frame of type I bipolar disorder,[53–55] and in this case no exacerbation of depressive symptoms was observed in the patients. Post-hoc analysis of these trials demonstrated statistically significant differences compared to the placebo for all 11 points of the Young Mania Rating Scale (YMRS), including the four main points (excited mood, irritancy, speech tempo and quantity, and aggressive behavior).[56] The effect size varied within the range of 0.31 to 0.55 and was a maximum for "irritancy" point, which was common in clinical practice for patients with mania and mixed states.[56] These trials give evidence of cariprazine efficiency for treatment of the entire range of manic symptoms including mixed ones, which afforded the grounds for the United States Food and Drug Administration (FDA) to approve cariprazine for treatment of manic and mixed states in the frame of type I bipolar disorder in the US. Recently cariprazine has been also registered in Russia for the same indication.[49] In this sense, cariprazine administered jointly with haloperidol, olanzapine, risperidone, or quetiapine is recommended in mania treatment algorithms for bipolar disorder.[57] On the other hand, at present, cariprazine is the second antipsychotic drug of choice after quetiapine approved for maintenance therapy of depressive, manic, and mixed episodes in the frame of type I bipolar disorder.

The recommended dose range for this indication in Russia is 3–6 mg.[49] The initial dose of 1.5 mg may be increased to 3 mg as early as the second day of treatment and further to 6 mg per day depending on the clinical response. Generally, rapid increase of the dose and the necessity to use maximum doses of the drug for treatment of manic states is also typical for other antipsychotic agents, for example, quetiapine and aripiprazole. It is believed that use of the optimal dose of cariprazine for the treatment of depression (1.5 mg) may be insufficient for the prevention of mania.[56] Thus, the use of higher doses of cariprazine (4.5–6 mg) with an initial rapid increase in dose is reasonable for treatment of schizophrenia with a high proportion of manic states.

EFFECT OF CARIPRAZINE ON THE DOMAIN "PSYCHOMOTOR SYMPTOMS"

The ICD-11 domain "Psychomotor Symptoms of Primary Psychotic Disorders" mainly includes, but is not limited to, catatonic symptoms, particularly psychomotor agitation, psychomotor retardation, negativism, and posturing.[7] The modern schizophrenia treatment algorithms recommend electroconvulsive treatment or combination of lorazepam and a second-generation antipsychotic drug with low risk of the development of neuroleptic malignant syndrome as the first-line treatment in cases of catatonic symptoms or catatonic schizophrenia,[52,58] especially when there is a high proportion of such symptoms as mutism, grimacing, staring, and disengagement.[59]

As no increase in the risk of neuroleptic malignant syndrome development during cariprazine administration is observed in the course of any acute[21] and maintenance[60] therapy stages for patients with schizophrenia, the combination of lorazepam and cariprazine in this case may be considered a possibility for the treatment of these states. Besides, analysis of changes in individual PANSS points that are similar to catatonic symptoms in their structure (within the psychopathological meaning) evidences the statistically significant difference between cariprazine and the placebo in relation to the majority of symptoms, particularly (N7) stereotyped thinking (effect size of 0.23), (G5) mannerism and posturing (effect size of 0.15), and (G14) lack of impulsivity control (effect size of 0.15).[22] Nevertheless, given our present knowledge about this state, the role of antipsychotic drugs in general, and cariprazine in particular, for the treatment of catatonic symptoms is not so significant as it seemed previously.

EFFECT OF CARIPRAZINE ON THE DOMAIN "COGNITIVE SYMPTOMS"

The neurocognitive deficit in cases of schizophrenia can be associated with the worst prognosis for the disease, reduction of functioning, and is often otherwise related to negative symptoms.[61,62] Neurocognitive deficit is the most prominent of the long-term stages of the disease.[63] The significance of the cognitive symptoms for schizophrenia diagnostics in ICD-11 was enhanced, and the domain "Cognitive Symptoms of Primary Psychotic Disorders", including the information processing rate, attention/concentration, orientation, abstract thinking, verbal or visual learning, and working memory, was introduced.[7] In the course of pre-clinical trials, cariprazine demonstrated its efficiency in relation to cognitive dysfunction.[64] Evidence of the positive effect of cariprazine on the cognitive functions

is available. In particular, cariprazine in a dose of 1.5–9 mg demonstrated medium-to-high effect size (0.47) for the domain Disorganization of thinking (Points N5, G5, G10, G11, G13, G15, P2), also including the symptoms of neurocognitive disorder such as "Difficulty in abstract thinking" (N5), effect size 0.26; "disorientation" (G10), effect size 0.26; "Poor attention" (G11), effect size 0.36; and "conceptual disorganization" (P2), effect size 0.44.[22,63] Insufficient effect size (0.15) was only observed for the point "mannerism and posturing" (G5).[22] Improvement of cognitive symptoms was also noted in a comparison of cariprazine with risperidone:[31] by the end of the twenty-sixth week of therapy, cariprazine was clearly superior to risperidone with regard to the PANSS factors identified related to cognitive functions in a statistically significant manner. Hence, this parameter in relation to the Marder factor for disorganized thoughts[5] was -4.16 vs. -3.53 (p=0.05), and for the Meltzer cognitive sub-scale[65] including the PANSS points N5, N7, P2, G10, and G11 it was -3.13 vs. -2.60 (p=0.028) in favor of cariprazine, respectively.[32] Besides, it was demonstrated that administration of cariprazine in a dose of 3 mg to patients with basic attention impairment resulted in statistically significant (as compared with the placebo) improvement of attention strength and stability, as measured via the CDR (Cognitive Drug Research) test.[20] Thus, in accordance with the initial hypothesis on the potential pro-cognitive effect of cariprazine, this drug has sufficient efficiency in relation to neurocognitive symptoms and which does not depend on any other symptoms (positive, negative, or depressive) and exceeds the relevant efficiency of other antipsychotic agents, for example risperidone. On the other hand, psychological interventions, primarily cognitive remediation, as well as their combinations with psycho-social and rehabilitation approaches, take the lead in modern schizophrenia treatment algorithms for correction of cognitive deficits, while the roles and positions of antipsychotic agents in the treatment of cognitive deficits are less significant.[53] Analysis of the PANSS points associated with neurocognitive disorder offers evidence of the pro-cognitive effect of this drug, especially in higher doses (4.5–6 mg).[22] On the other hand, additional trials with the use of standardized banks of neurocognitive tests are required in order to identify the particular neurocognitive disorder domains associated with this effect.

FUNCTIONAL IMPAIRMENT

According to DSM-5, the presence of functional impairment in one or more areas, such as work, inter personal relations, or self-care (Criterion B), is necessary for diagnosis of schizophrenia apart from the certain threshold of symptoms (Criterion A) and their duration (Criterion C).[8] Unfortunately, this criterion is not represented in ICD-11 or, indeed, in ICD-10, and diagnosis of schizophrenia are based solely on the clinical criteria.[7] On the other hand, neurocognition, positive symptoms, disorganization, and abulia have the most impact on the real functioning of patients with schizophrenia.[66] It is important that therapy should not only result in a reduction of the particular symptoms but also an improvement in the functional outcomes of the disease. Analysis of the treatment of psychotic episodes with cariprazine within the framework of maintenance treatment of schizophrenia showed that cariprazine was superior to the placebo in the statistically reliable manner, not only for reduction of psychotic symptoms but also in terms of improving the patient's quality of life, as measured by the reduction in total score of the Schizophrenia-Specific Quality of Life Scale (SQLS), as well as the vitality factors and the psycho-social factor of this scale.[20,21] The conclusion drawn on this basis is that cariprazine administration can be associated with improved quality of life for schizophrenic patients from the first week up to the sixth week of therapy.[67] Post-hoc analysis of one of the cited studies[20] via the pro-social PANSS factor,[68] including Points G16, N2, N4, N7, P3, and P6, showed that the difference between cariprazine and the placebo was statistically significant for a dose of 3 mg as early as the first week of therapy, and for 6 mg from the third week of treatment.[67] A Statistical difference was observed for both cariprazine doses and the placebo in relation to emotional withdrawal (N2), passive/apathetic social withdrawal (N4), active social avoidance (G16), and suspicion/persecution (P6).[67] Post-hoc analysis of all short-term cariprazine trials suggests that the effect size for different doses of cariprazine, in relation to the pro-social PANSS factor, is 0.32, and is statistically significant for all points of this factor including hallucinatory behavior (0.2), and stereotyped thinking (0.23).[22]

Post-hoc analysis of cariprazine treatment in the frame of maintenance treatment of schizophrenia showed that transition to placebo for stable patients within

the framework of the 72-week double blind trial was associated with considerable deterioration of psycho-social functioning, as measured via the Personal and Social Performance Scale (PSP),[69] while it remained unchanged in the cariprazine group with statistically significant differences in favor of cariprazine both in relation to the total score as per the PSP Scale and all its domains (socially useful activities; relations with relatives and friends; self-care; aggressive behavior).[67] These results correlate with the comparative study results for cariprazine and risperidone,[31] where not only statistically significant reduction of the total score according to the PSP Scale has been observed in the cariprazine group by the end of the twenty-sixth week of therapy and beginning as early as the tenth week, but more prominent improvement of three out of four domains of the PSP Scale (socially useful activities; relations with relatives and friends; self-care) have also been noted, which correlate with daily activities and better therapy commitment.[70] Thus, one might draw the conclusion that cariprazine administration is associated not only with efficiency in relation to various schizophrenia domains but also with improvement in psycho-social functioning in the course of both the acute and preventive schizophrenia treatment stages.

CARIPRAZINE TOLERABILITY AND SAFETY

The tolerability and side effects of the new antipsychotic agent were also studied in the course of pre-approval double-blind placebo-controlled multi-center trials of acute treatment, in addition to determining its efficiency.[19–21] The side effects in the cariprazine group included insomnia, extrapyramidal symptoms, akathisia, sedation, nausea, dizziness, and constipation at least twice as often as in the placebo group. Higher doses of cariprazine resulted in additional efficiency of the drug without any increase of the frequency of any side effects. The severity of akathisia, extrapyramidal syndrome, and tremor manifestation was usually quite mild, and more frequent among patients taking higher doses of the drug. Metabolic syndrome was low in both groups; in particular, weight gain by more than 7% was observed in 8% of the patients taking 3–6 mg of cariprazine, 11% of the patients taking 6–9 mg, and 4% of the patients taking the placebo.

The study of safety and tolerability of different doses of cariprazine (3, 6, and 9 mg) for stable patients with schizophrenia lasting for 72 weeks within the framework of the non-blind trial phase showed that akathisia (19.2%), insomnia (14.4%), and headache were the most frequent side effects. Within the framework of the placebo-controlled stage of this trial, such side effects as akathisia (5% and 3%, respectively), extrapyramidal syndrome (5.9% and 3%, respectively), tremor (7.9% and 0%, respectively) and backache (5% and 2%, respectively) were reliably more frequent in the cariprazine group.[24]

The tolerability and safety of various doses of cariprazine were also confirmed in the course of two non-blind trials lasting for 1 year[61] and 48 weeks.[35] Akathisia (16%), headache (13%), insomnia (13%), and weight gain of 1.5 kg on average (10%) were the most frequent side effects in the first trial (the dose of cariprazine was 3–9 mg, *n*=586), and the prolactin level decreased slowly in this case.[61] In the course of the second trial (the dose of cariprazine was 1.5–4.5 mg, *n*=93), such side effects as akathisia (14%), insomnia (14%), and weight gain of 1.9 kg on average were observed.[35] None of the treatments were terminated due to changes in metabolic parameters or body weight were registered. No changes in cardiovascular parameters were observed in the patients treated with cariprazine. Post-hoc analysis of these two trials showed that akathisia and the psychotic state recrudescence were the only causes of treatment termination.[36] Akathisia (19.6%), which more frequent within a dose range of 1.5–3 mg per day, insomnia (13.3%) for a dose of 9 mg, and headache (12.8%) for a dose of 1.5–3 mg, were the most common for patients treated with cariprazine. Prolactin levels were reduced in patients of all groups. Extrapyramidal syndrome was observed in 6.6% of the patients with approximately the same frequency in the different groups. Weight gain of ≥7% was observed in 34% of patients of normal weight, and more frequently for higher doses. This trial also demonstrated that adherence to the recommended doses (1.5–6.0 mg) in clinical practice was reasonable, and any dose increase did not generally result in an increased number of side effects and higher withdrawal of the patients from the trial.[36]

DISCUSSION

In the course of our review, we have studied the efficiency of cariprazine for treatment of six of the schizophrenia symptom domains identified in ICD-11. At present, cariprazine has been approved for schizophrenia treatment within the framework of acute and maintenance

treatment including in the US, the EU countries, and Russia. Further, it has been approved in some countries (the USA, Russia) for acute treatment of manic, mixed states and depression in the frame of type I bipolar disorder.

Analysis of the randomized controlled trial of cariprazine use for schizophrenia treatment based on analysis of the PANSS scale points enables one to conclude that the drug is efficient for the treatment of various positive symptoms, including delusion, hallucination, and abnormal behavior both within the framework of acute and maintenance therapy of schizophrenia for patients suffering their first psychotic episode, and with multiple ones. Although cariprazine took a medium position among all antipsychotic agents with regard to the reduction of delusions and hallucinations it has a positive effect on other schizophrenia symptoms associated with positive syndromes, mainly the secondary negative symptoms such as disorganization of thinking and depression, and also demonstrates a favorable profile of side effects. On the other hand, cariprazine has a positive effect on other schizophrenia symptoms associated with positive syndromes, mainly the secondary negative symptoms such as disorganization of thinking and depression, and also demonstrates a favorable profile of side effects. Moreover, the modern schizophrenia treatment algorithms should focus on the safety of the drug rather than on its efficiency. Taking into account the above, cariprazine should be considered one of the preferred drugs for schizophrenic patients with dominating delusion and hallucination. In addition, the high effect size of cariprazine in the reduction of disorganized thinking symptoms and its proven, direct impact on the signs of aggressiveness and hostility make cariprazine one of the principal front-line drugs for all positive symptom groups noted in ICD-11. In case of apparent agitation and excitement in schizophrenic patients, it is recommended that benzodiazepine or any other sedative antipsychotic agent, for example, clozapine, quetiapine, or olanzapine, or an antihistamine drug be added to the treatment.[31]

For diagnostics of the updated symptoms within the ICD-11 domain "Negative Symptoms", it is necessary not only to detect them in the mental state of a schizophrenic patient but also to demonstrate that they do not stem from any other causes (secondary negative symptoms).[8] To date, it has been demonstrated that only two antipsychotic agents have a primary anti negative effect (amisulpride and cariprazine). However, taking into account other factors, particularly the side effect profile and availability of the trial on direct comparison with another antipsychotic agents (risperidone) for schizophrenic patients with prevailing negative symptoms in the course of long-term therapy, cariprazine is nevertheless considered the first-line drug for schizophrenic patients with dominant negative symptoms.

According to ICD-11 diagnostics of depressive symptoms for patients with schizophrenia, there should be a focus on the evaluation of mood and suicidal thoughts as other typical depressive symptoms, including anhedonia and retardation, overlap with the negative symptoms. Minimum or statistically insignificant differences between cariprazine and the placebo in reduction of the total score for the PANSS points "depression" (G6) and "guilt feelings (G3)" within the framework of Acute treatment of schizophrenia were obtained. Based on randomized clinical trials, at present it is difficult to discuss the advantages of cariprazine in comparison with other second-generation antipsychotic agents for the treatment of depression in cases of schizophrenia. On the other hand, frequent development of depressive episodes within the post-psychotic period and the proven efficiency of cariprazine in treatment of bipolar depression may potentially make cariprazine the front-line drug for such a cohort of patients, although this hypothesis requires additional studies.

There are no substantial differences in description of the ICD-11 domain "Manic Symptoms of Primary Psychotic Disorders" and the main (core) criteria of a manic episode, except for the indication that enhancement of psychomotor activity should be considered in another ICD-11 domain.[7] In this sense, the studies on the proven antimanic efficiency of cariprazine in cases of bipolar disorder may be extrapolated to the treatment of schizophrenic patients with apparent manic symptoms but without any signs of psychomotor agitation. On the other hand, at present, the inventory of any doctor contains various drugs for the treatment of manic states, and tolerability should apparently be the focus with regard to the selection of any particular drug. Certain advantages related to cariprazine in comparison with other antimanic agents are observed for schizophrenic patients with metabolic syndrome as well as those with a potential bipolar pattern of the disease, for example,

the presence of manic and depressive episodes in the case history.

The modern treatment algorithms for catatonic symptoms in the cases of schizophrenia considered in ICD-11 within the framework of the domain "Psychomotor Symptoms of Primary Psychotic Disorders" propose benzodiazepines (mainly lorazepam) and electroconvulsive therapy as the first-line treatment, and the role of antipsychotic drugs here is secondary and possible only in combination with lorazepam. In this sense, the combination of lorazepam and cariprazine may be a possible option, together with the use of antipsychotic agents with a low risk of causing the development of neuroleptic malignant syndrome.

Inclusion of the domain "Cognitive Symptoms of Primary Psychotic Disorders" in ICD-11 has confirmed the importance of these symptoms for diagnostics, prediction, and therapy of schizophrenic patients as they become leading at the long-term stages of the disease. The pro-cognitive effects of cariprazine, independent of any other symptoms and supposed on the basis of the drug receptor profile analysis and animal studies, was confirmed for schizophrenic patients within the framework of short-term and long-term therapy stages, and exceeded the same effects of other drugs, particularly risperidone. This effect was primarily observed by analysis of changes in the "cognitive" points of the PANSS scale, and further studies with the use of the tools for precise evaluation of different neurocognitive disorder components, including memory, attention, psychomotor ability rate, and executive functions, should demonstrate the efficiency of cariprazine in this area.

Improvement of functioning for patients with schizophrenia does not always correlate with a statistically significant reduction of positive, negative, or cognitive symptoms of the disease, and the necessity to verify functional impairment in one or several areas is an important stage of the diagnostic process in some international classifications of diseases.[7] Subsequent to randomized clinical trials, cariprazine demonstrated the capability to improve the functioning of schizophrenic patients, regardless of the effect on the disease symptoms, based both on the reduction of the "pro-social" PANSS points and positive impact on the various components of the Personal and Social Performance Scale (PSP) that are valid for these purposes.

Such side effects as akathisia, extrapyramidal syndrome, insomnia, and slight weight gain were the most frequent issues observed during cariprazine therapy. As a rule, these symptoms were mild and did not require termination of treatment, although additional drugs had to be prescribed in some cases. In particular, addition of benzodiazepine, for example, lorazepam and clonazepam or propranolol[53] is the front-line therapy in cases of akathisia, whilst addition of benzodiazepine, an antihistamine drug, trazodone or a sedative antipsychotic agent[29] should be considered in cases of insomnia.

Implementation of the ICD-11 schizophrenia domains in clinical practice can face certain difficulties. In particular, as the diagnostics of the schizophrenic spectrum disorders have focused on detection of psychotic and negative symptoms for many years, there is some concern that other domains will only be evaluated by clinicians in cases of their severe manifestation. Besides, it is highly probable that clinicians will often use Point 9 ("evaluation is impossible on the basis of the available data") in the compressed time frame for evaluation of various domains, except for the most obvious ones (psychotic, manic) that can depreciate dimensional assessment. The necessity to develop particular tools (questionnaires, scales) for rapid evaluation is one of the possible options to facilitate the transition to the full implementation of the schizophrenia symptom domains identified in ICD-11 at the global level. This is especially relevant for the evaluation of the degree of cognitive deficits as it is difficult for practitioners in the course of the clinical interview. It should be also explained to doctors how often they have to evaluate the domains at different stages of care, when to begin the treatment, or whether dynamic observation is sufficient. Proactive efforts to enhance the psychiatric community's awareness of the advantages of this classification in the clinical practice and development of training programs on its application for different target audiences are required.[10]

The online survey of European clinicians and researchers engaged in the treatment of schizophrenic patients enabled the identification of the states in the frame of schizophrenia where use of cariprazine might be considered the first-line therapy: the first psychotic episode, positive symptoms, negative symptoms, psychomotor agitation (in combination with other drugs,

for example, benzodiazepine), presence of metabolic syndrome, and comorbid drug abuse.[29]

Absence of any studies into the use of the schizophrenia symptom domains identified in DSM-5/ICD-11 to evaluate the efficiency of antipsychotic agents, including cariprazine, should be considered the main limitation to the present review. The majority of studies comparing cariprazine with a placebo and/or other antipsychotic agents used different PANSS sub-scales or clusters of symptoms only partially corresponding to all schizophrenia domains, as per DSM-5/ICD-11. Analysis of the PANSS scale points enables the evaluation of the ICD-11 domains "Positive Symptoms", "Manic Mood Symptoms", and "Psychomotor Symptoms" with a sufficient degree of accuracy. At the same time, the direct correlation between the PANSS points and other ICD-11 domains ("Negative Symptoms", "Depressive Mood Symptoms", "Cognitive Symptoms") is not always apparent. Other tools, for example, the Brief Negative Symptom Scale (BNSS),[71] the Calgary Depression Schizophrenia Scale (CDSS),[42] or the Brief Scale Assessment of Cognition in Schizophrenia (BACS),[72] should be involved due to their more precise evaluations in any future studies. Scarcity of independent trials for the comparison of cariprazine's efficiency and tolerability with placebos and/or other antipsychotic agents without any participation of the company producing this drug should also be pointed out.

CONCLUSION

It was demonstrated in the present review — through the example of cariprazine, an antipsychotic agent — that the implementation of the identified ICD-11 domains into clinical practice might facilitate the development of more individualized approaches to therapy and the improvement of quality of care for schizophrenic patients. Cariprazine is the first-line drug for treatment of the ICD-11 domain "Negative Symptoms" as well as front-line therapy for the treatment of the domains "Positive Symptoms" and "Cognitive Symptoms". Additional studies are required in order to evaluate the effect of cariprazine on the ICD-11 domains "Manic Mood Symptoms" and "Depressive Mood Symptoms". Application of cariprazine monotherapy for the domain "Psychomotor Symptoms" is not considered reasonable. Cariprazine results in improved functioning of patients with schizophrenia. Additional tools should be implemented in clinical practice that enable doctors to evaluate schizophrenia domains in their clinical practice both rapidly and reliably.

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